

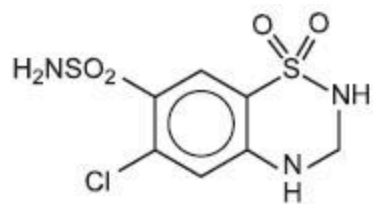
HYDROCHLOROTHIAZIDE - hydrochlorothiazide tablet

International Labs, Inc.

DESCRIPTION

DESCRIPTION

Hydrochlorothiazide is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. It is chemically designated as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and it has the following structural formula:Enter section text here



C₇H₈ClN₃O₄S₂

M.W. 297.74

Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water, but freely soluble in sodium hydroxide solution. Each tablet for oral administration contains 25 mg or 50 mg hydrochlorothiazide. In addition, each tablet contains the following inactive ingredients: dibasic calcium phosphate, lactose monohydrate, pregelatinized starch, FDC yellow No. 6 lake, corn starch, colloidal silicon dioxide, and magnesium stearate.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure.

Hydrochlorothiazide affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are

approximately equal in their diuretic efficacy.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by

some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics and Metabolism

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours,

the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within

24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE

INDICATIONS AND USAGE

Hydrochlorothiazide tablets are indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and

corticosteroid and estrogen therapy.

Hydrochlorothiazide tablets have also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute

glomerulonephritis, and chronic renal failure.

Hydrochlorothiazide tablets are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy

Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not

prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy.

Thiazides

are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see

PRECAUTIONS,

Pregnancy). Dependent edema in pregnancy, resulting from restriction of venous return by the gravid uterus is properly treated through

elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is illogical and

unnecessary. During normal pregnancy there is hypervolemia which is not harmful to the fetus or the mother in the absence of cardiovascular

disease. However, it may be associated with edema, rarely generalized edema. If such edema causes discomfort, increased recumbency will

often provide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic

therapy may provide relief and be appropriate.

CONTRAINDICATIONS

CONTRAINDICATIONS

Anuria.

Hypersensitivity to this product or to other sulfonamide-derived drugs.

WARNINGS

WARNINGS

Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug

may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid

and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics (see **PRECAUTIONS, Drug Interactions**).

PRECAUTIONS

PRECAUTIONS

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic

alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively

or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth,

thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria,

tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when

severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may

also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Hypokalemia may

be avoided or treated by potassium sparing diuretics or potassium supplements such as foods with a high potassium content.

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as

in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may

occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances

when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide

diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence

of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be

discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Laboratory Tests

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Drug Interactions

When given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics

Potential of orthostatic hypotension may occur.

Antidiabetic drugs - (oral agents and insulin)

Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs

Additive effect or potentiation.

Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol

resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)

Possible increased responsiveness to the muscle relaxant.

Lithium

Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer

to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide.

Non-steroidal Anti-inflammatory Drugs

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive

effects of loop, potassium-sparing and thiazide diuretics. Therefore, when hydrochlorothiazide and non-steroidal anti-inflammatory agents

are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function (see **PRECAUTIONS, General**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of

a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at

doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepato-carcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA100, TA 1535, TA

1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell

chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results

were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays,

using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified

concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via

their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy**Teratogenic Effects – Pregnancy Category B**

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis

at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly

other adverse reactions that have occurred in adults.

Nursing Mothers

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made

whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use

There are no well-controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients. (See **DOSAGE AND ADMINISTRATION, Infants and Children**).

ADVERSE REACTIONS

ADVERSE REACTIONS

The following adverse reactions have been reported and, within each category, are listed in the order of decreasing severity.

Body as a whole

Weakness

Cardiovascular

Hypotension including orthostatic Hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs)

Digestive

Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia

Hematologic

Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity

Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura

Metabolic

Electrolyte imbalance (see **PRECAUTIONS**), hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal

Muscle spasm

Nervous System/Psychiatric

Vertigo, paresthesias, dizziness, headache, restlessness

Renal

Renal failure, renal dysfunction, interstitial nephritis (see **WARNINGS**)

Skin

Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia

Special Senses

Transient blurred vision, xanthopsia

Urogenital

Impotence

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

OVERDOSAGE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hyponatremia, hypochloremia)

and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed.

Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial

respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

HOW SUPPLIED

HOW SUPPLIED

Hydrochlorothiazide Tablets USP, 25 mg are light pink colored, round shaped, flat faced beveled edge uncoated tablets, debossed with 'D'

and '27' on one side separated by scoring and plain on the other side.

Shellpaks® of 30 tablets NDC 54458-939-10

PHARMACIST: Dispense in a well-closed container as defined in the USP. Use child-resistant closure (as required).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:

LI0023

DOSAGE AND ADMINISTRATION

pound (3 mg/kg) per day in two divided doses may be required. (See **PRECAUTIONS, Pediatric Use**).

LB0143 - HYDROCHLOROTHIAZIDE TABLETS, USP 25 mg

NDC 54458-939-10

Hydrochlorothiazide

Tablets, USP

25 mg

Rx only

See the accompanying drug information
sheet for full drug information

Depress tab and pull dosage card out
DO NOT SEPARATE FROM PLASTIC SHELL

**Contains one dosage card
of 30 tablets**

25 mg 25 mg 25 mg 25 mg

Each tablet contains:
Hydrochlorothiazide USP 25 mg.

WARNING:

KEEP OUT OF THE REACH OF CHILDREN

TAMPER-EVIDENT: Do not use this product if plastic shell is not intact, blister backing appears to be disturbed, or if individual blister units are broken or torn.

CHILD-RESISTANT: Do not separate dosage card from protective plastic shell. Return card to case after use.

Dispense in a well-closed container as defined in the USP.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:
Aurobindo Pharma Limited
Hyderabad-500 072, India

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International Labs, Inc.
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Bentonville, AR 72716

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LB0143
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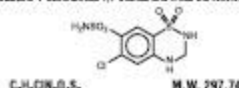
LI0023 - HYDROCHLOROTHIAZIDE TABLETS, USP 25 mg - PATIENT PACKAGE INSERT

Hydrochlorothiazide Tablets, USP

Rx only

DESCRIPTION

Hydrochlorothiazide is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. It is chemically designated as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide and has the following structural formula:



Hydrochlorothiazide is a white, crystalline powder which is slightly soluble in water, but freely soluble in sodium hydroxide solution. Each tablet for oral administration contains 25 mg or 50 mg hydrochlorothiazide. In addition, each tablet contains the following inactive ingredients: basic calcium phosphate, lactose monohydrate, pregelatinized starch, FD&C yellow No. 6 lake, corn starch, colloidal silicon dioxide, and magnesium stearate.

CLINICAL PHARMACOLOGY

The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure. Hydrochlorothiazide affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy.

Hydrochlorothiazide increases secretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics and Metabolism

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 7.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental barrier and the blood-brain barrier and is secreted in breast milk.

INDICATIONS AND USAGE

Hydrochlorothiazide tablets are indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Hydrochlorothiazide tablets have also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

Hydrochlorothiazide tablets are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy

Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pathological causes or from the physiological and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathological causes. Just as they are in the absence of pregnancy (see PRECAUTIONS, Pregnancy). Concomitant edema in pregnancy, resulting from retention of water of return by the placenta is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in the toxemia is logical and unnecessary. During normal pregnancy there is hypovolemia which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However, if it may be associated with edema, rarely generalized edema. If such edema causes discomfort, increased natriuresis will often provide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic therapy may provide relief and be appropriate.

CONTRAINDICATIONS

Anuria

Hypersensitivity to this product or to other sulfonamide-derived drugs.

WARNINGS

Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance. Namely, in particular, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is receiving concomitantly or receiving potent diuretics. Warning signs or symptoms of fluid and electrolyte imbalances, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypokalemia, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis. When severe chloride is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by potassium sparing diuretics or potassium supplements such as foods with a high potassium content.

Although any chloride deficit is generally mild and usually does not require specific treatment except a diet rich in potassium (see PRECAUTIONS, General), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypotension may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hypoglycemia may occur with thiazide diuretics. These latent diabetic mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Laboratory Tests

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Drug Interactions

When given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics

Potential of orthostatic hypotension may occur.

Antihypertensive drugs—(oral agents and insulin)

Dosage adjustment of the antihypertensive drug may be required.

Other antihypertensive drugs

Additive effect or potentiation.

Cholinergic and vagolytic agents

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cationic exchange or cationic resin bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Cardiovascular, CNS

Intensified electrolyte depletion, particularly hypokalemia.

Protein anuria (e.g., nephropathy)

Possible decreased response to protein anuria but not sufficient to preclude their use.

Skeletal muscle relaxants, antispasmodics (e.g., tubocurarine)

Possible increased responsiveness to the muscle relaxant.

Lithium

Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide.

Non-steroidal Anti-Inflammatory Drugs

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS, General).

Contraception, Sterilization, Impairment of Fertility

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepato-carcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. *In vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and in *in vivo* assays using lymphocytes and in the Mouse Lymphoma (CL) mutagenicity assay, using concentrations of hydrochlorothiazide from 43 to 1500 mg/mL, and in the *in vivo* micronucleus assay (a micronucleus assay) at an unsupervised concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and through gestation.

Pregnancy

Reproductive Effects—Pregnancy Category B

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis

ADVERSE REACTIONS

The following adverse reactions have been reported and, within each category, are listed in the order of decreasing severity.

Body as a whole

Weakness

Cardiovascular

Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics and hypotensive drugs)

Digestive

Parosmia, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, cholelithiasis, cramping, constipation, gastric irritation, nausea, anorexia

Hematologic

Aplastic anemia, agranulocytosis, leukopenia, hemoglobinemia, thrombocytopenia

Hypersensitivity

Anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonia and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura

Metabolic

Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hypernatremia

Musculoskeletal

Muscle spasms

Nervous System/Psychiatric

Vertigo, parosmia, dizziness, headache, restlessness

Local

Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS)

Skin

Erythema multiforme including Stevens-Johnson syndrome, acraliform dermatitis including toxic epidermal necrolysis, alopecia

Special Senses

Transient blurred vision, anisopsia

Frequent

Impotence

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSEAGE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD₅₀ of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

DOSE AND ADMINISTRATION

Thiazides should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

Adults

For Edema

The usual adult dosage is 25 to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or three to five days each week. With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalances are less likely to occur.

For Control of Hypertension

The usual initial dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses. Doses above 50 mg are often associated with marked reductions in serum potassium (see also PRECAUTIONS).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

Infants and Children

For Edema and For Control of Hypertension

The usual pediatric dosage is 0.5 to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 57.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required. (See PRECAUTIONS, Pediatric Use).

HOW SUPPLIED

Hydrochlorothiazide Tablets USP, 25 mg are light pink colored, round shaped, flat faced beveled edge a beveled edge a beveled edge, debossed with "D" and "27" on one side separated by scoring and plain on the other side.

Shelfpacks® of 30 tablets NDC 54458-059-10

PARAMATCH®: Digoson is a well-closed container as defined in the USP. Use child-resistant closure (as required).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured by:
Aurobindo Pharma United
Hydrex-500 072, India
Packaged by:
Informative LLC, Inc.,
St. Petersburg, FL 33710
Distributed by:
West-War
Berkshire, AR 72716

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